REMARKS

In response to the Official Action mailed October 30, 2003, Applicants respectfully request that the Examiner reconsider the rejection of the remaining claims.

Claims 5, 7, and 14-22 are withdrawn.

Claims 1-4, 6, and 8-13 remain.

Claims 1 and 10-13 are being amended.

Claims 10-13 stand rejected under 35 U.S.C. § 101(b) because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. The Applicants have amended Claims 10-13 to appropriately recite methods including steps involved in the process.

Claims 1-4, 6, and 8-13 stand rejected under 35 U.S.C. §102(a) as being anticipated by *Mascheretti, et al.(* Gastroenterology, April 2001, Vol. 120, No. 5, Suppl. 1 pg. A-68) (hereinafter, "the *Mascheretti* reference"). The rejections should become moot by filing the certified copy of the priority application and the Katz-type declaration. The European priority application was filed before the publication date of the *Mascheretti* reference, and thus the *Mascheretti* reference should not be considered as a basis for rejection.

Claims 1-5, 6, and 8-13 stand rejected under 35 U.S.C. §112, second paragraph, because the specification does not reasonably provide enablement. Applicants respectfully traverse these rejections.

The Examiner submits that in the specification, there are only working examples for the embodiment wherein anti-TNF-therapy is infliximab therapy, the disease is Crohn's disease, and the SNP is nucleotide substitution A/G at position 168 from the transcription starting site in exon 2 of the gene coding for the TNF Receptor II. The Examiner has also noted that the claims, before amendment, however, claim embodiments to any anti-TNF-therapy, any SNP in the gene coding for the TNF Receptor II, and any disease.

Furthermore, the Examiner submits the present invention belongs to "the unpredictable arts such as chemistry and biology." The Examiner has cited several documents relating to polymorphisms and their association to diseases in order to support the proposition that a high degree of unpredictability exists in the technical field of the present invention. In view of this alleged unpredictability it is believed by the Examiner that undue experimentation is required to apply the method of the invention to the broadly claimed embodiments, and it is regarded uncertain whether there would be any success.

Applicants respectfully submit that the Examiner's view is, however, not correct. As an initial matter, the Examiner cites a number of relatively insignificant and sub-average studies. The cited studies either suffer from an improper selection of patients or were performed with an insufficiently low number of patients. The negative examples therein differ from applicant's findings in many respects. For example, the population of patients examined according to the present invention was defined very restrictively, the statement of the problem was clearly stated and the results were supported by a particularly expressive study design. Theoretically only a limited number of polymorphisms was measured in a distinct phenotype (responding or non-responding to anti-TNF-therapy).

Applicants also respectfully note that the relation between genetic and complex phenotype is considerably more complicated than expressed by the Examiner. Among other things, in polygenic disposition models there are no equivalences between one single disease gene and a disease, however, the correlations are statistically substantially more manifold, and therefore highly validated phenotypes (as documented in the invention under conditions of "good clinical practice") and very robust designs (as by the prospective trial according to the invention) are required for exploitation.

Moreover, the analysis of the genetical state of the art by the Examiner is not complete. For example, important conceptions like linkage disequilibrium are ignored or are not applied. There is, for example, the lack of full consideration of polygenic diseases and disease associations and pharmacogenetic effects are mixed up. Please

note, that there is no correlation of genesis of Crohn's disease and the described polymorphism.

Further, please note that genetic exploration yields predictable and reproducible results also in the case of complex diseases. This is for example proved by the article regarding the first disease gene for Crohn's disease published by *Hampe et al.* in The Lancet 2001. This finding was reproduced many times in the world literature (and was published at the same time by *Hugot et al.* and *Ogura et al.* in Nature 2001).

In the Examiner's comments regarding the post filing date art (Page 9 of the Office Action) have similar deficiencies, similar to those outlined above. The Examiner is, however, correct insofar as there is a difference between anti-TNF-therapy in general and the specific anti-TNF-therapy with a TNF-binding protein like infliximab. Therapies with pentoxifylline or thalidomide are also anti-TNF-therapies in a certain respect, however, fundamentally different from therapy with TNF-binding protein. Therefore, the claims have been amended and directed more clearly to an anti-TNF-therapy with a TNF-binding protein.

The phenomenon of non-response to anti-TNF-treatment is generic for anti-TNF-therapy of TNF-driven diseases, and therefore independent of a specific disease, and theoretically also independent of the kind of TNF-binding protein.

Applicants therefore do not believe either that further working examples are necessary in order to provide sufficient guidance for the skilled person. There are clear instructions in the scientific literature describing how pharmacogenetic findings may enter into therapy, and the respective experiments are standard in clinical trials or in the utilization of medicaments in large groups of patients.

In view of the above remarks, Claim 1-4, 6, and 8-13 should now be in condition to pass to issue. No new matter has been added to the present application.

Applicants herewith submit another Certified Copy of the priority document, European Patent Application No. 00 114 786.7.

Applicants determine that no additional fee is due. However, the Director is hereby authorized to charge any additional fees or credit any overpayment to Deposit Account Number 23-2426 of WINSTEAD SECHREST & MINICK P.C.

If the Examiner has any questions or comments concerning this paper or the present application in general, the Examiner is invited to call the undersigned at (214) 745-5374.

Respectfully submitted,
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